REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1-5, 8-14, 17-23, 26-33, 35, 37, 39, 42, 45-47 are pending after entry of the amendments set forth herein.

Claims 1-15, 17-40 and 42-47 were examined. Claims 1-15, 17-40 and 42-47 were rejected.

Please replace claims 1, 3-14, 17-23, 26-33, 35, 37, 39, 42, 45-47 with the clean version provided above. Claims 7, 15, 24-25, 34, 36, 38, 40 and 43-44 have been cancelled.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE.**"

Support for the amendments to claims directed to a targeting construct and methods of producing the targeting construct can be found throughout the specification at, for example, pages 55-59, specifically, Examples 1-4. Additionally, support for amendments to claims directed to murine embryonic stem cells, transgenic mice exhibiting a homozygous disruption in cGMP phosphodiesterase alpha subunit gene and methods of producing said transgenic mice and cells isolated from said mice may be found throughout the specification, at, for example, page 2, lines 3-18, page 7, lines 14-17 and page 21, lines 18-19. Also, support for claims directed to methods of identifying agents may be found throughout the specification at, for example, page 25, lines 18-29 and page 39, lines 16-35. No new matter is added by these amendments. As such, entry of the above amendments is respectfully requested.

The drawings have been corrected to comply with the objections set forth in PTO-948. Specifically, Figure 3B has been relabeled as "Figure 3B-1" and "Figure 3B-2." Further, the margins and character of the lines, numbers and letters have been amended in compliance with the Draftperson's review. A paper copy of the drawings is filed under a separate paper with a transmittal letter addressed to the Drawing Review Branch.

Pursuant to form PTO-948 and under 37 C.F.R. § 1.312 the specification, at the Brief Description of the Drawings paragraph, has been amended to properly identify Figures 3B-1 and 3B-2. No new matter is added by these amendments. As such, entry of the above amendments is respectfully requested.

The amendments to the claims, specification and drawings are made without prejudice to the pending or now cancelled claims or to any subject matter pursued in related applications. Moreover, the amendments are made solely to expedite prosecution of the application and are not intended to limit the scope of the invention. Applicants reserve the right to prosecute any cancelled subject matter at a later time or in a later filed divisional, continuation or continuation-in-part application.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Rejection under 35 U.S.C. § 112, 1st Paragraph.

The Office Action asserts that claims 1-15, 17-40 and 42-47 lack enablement "because the specification, while being enabling for a transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene, does not reasonably provide enablement for any transgenic animal and any knockout animal containing an altered allele for the cGMP phosphodiesterase gene." As such, the Applicants have incorporated the term "murine" or "transgenic mouse" into the relevant claims.

The Office Action also asserts that "the specification and the working examples provide sufficient guidance to practice the invention with only a homozygous, knockout mouse." The Applicants have thus incorporated the term "homozygous" to describe the type of disruption of a cGMP phosphodiesterase gene into the relevant claims.

It is also asserted in the Office Action that the specification "is not enabling for transgenic and/or knockout animals that exhibit no phenotype or that exhibit transgene-dependent phenotypes other than that disclosed in the instant specification." The Applicants have thus incorporated an eye abnormality phenotype or a hyperactive phenotype into the above-mentioned claims.

The Applicants submit that the rejections are overcome by the amendments. Applicants also submit that the amended claims are fully enabled by the teachings of the specification. Therefore, the Applicants submit that the rejection of above-cited claims under 35 U.S.C. § 112, first paragraph, is overcome in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 112, 2nd Paragraph.

Claim 1 has been rejected as being "incomplete for omitting essential steps." Specifically, the Office Action points out that "[c]laim 1 is drawn to a targeting construct comprising steps (a) through (d), wherein step (b) is missing."

The Applicants have amended claim 1 by re-lettering the steps so that the steps read in alphabetical order. Applicants submit that the newly amended claim 1 is definite and particularly points out and distinctly claims the subject matter regarded as the invention in accordance of 35 U.S.C. § 112, 2nd paragraph. The Examiner is thus respectfully requested to withdraw this rejection.

Rejection under 35 U.S.C. § 103(a).

Claims 1-15, 17-40 and 42-47 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Baehr et. al., FEBS letters vol. 278, no. 1 pp. 1070114 (1991), Lem et. al., Proc. Natl. Acad. Sci., USA, vol. 89, no. 10 pp 4422-4427 (1992) and further in view of Tanabe et. al., IOVS vol. 39, no. 4 pp S1118 (1998). Applicants respectfully point out that,

> "[t]o establish a proper prima facie case of obviousness, three basic criteria must be met. First, **there must be some suggestion or motivation**, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art**, to modify the reference or to combine reference teachings.** Second, there must be a reasonable expectation of success. Finally, **the prior art reference (or references when combined) must teach or suggest all the claim limitations.**"
>
> MPEP § 2142 *citing* In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Lem et. al. has been cited for its description that retinal degeneration is rescued in *rd* transgenic mice (i.e. mice with a disruption in the *rd* allele and display a retinal degeneration

phenotype) by expression of a cGMP phosphodiesterase **beta** subunit. Lem et. al. does not contain any teaching or suggestion of a transgenic mouse having a disruption in a cGMP phosphodiesterase **alpha** subunit gene. Thus, Lem et. al. fails to provide any suggestion or motivation to create the mouse of the present invention. Therefore, Lem et. al. is deficient in making the presently claimed invention obvious.

Tanabe et. al. has been cited for its description that phosphodiesterase **gamma** knockout mice may be used as a model for photoreceptor degeneration. Tanabe et. al. does not contain any teaching or suggestion of a transgenic mouse having a disruption in a cGMP phosphodiesterase **alpha** subunit gene. Thus, Tanabe et. al. fails to provide any suggestion or motivation to create the mice of the present invention. Thus, Tanabe et. al. is deficient in making the presently claimed invention obvious.

The disclosures of Lem and Tanabe are absent of any teaching or suggestion of disrupting the cGMP phosphodiesterase **alpha** subunit gene, and in particular, to produce the transgenic mice, targeting constructs, tissues, cells, and methods as recited in the pending claims. More particularly, the teachings of Lem and Tanabe, which are concerned with the **beta and gamma subunits** of cGMP phosphdiesterase, combined or alone, do not teach or suggest in any way the transgenic mice comprising a disrupted cGMP phosphodiesterase **alpha subunit** gene, wherein such transgenic mice exhibit eye abnormalities, methods of producing such transgenic mice, targeting constructs, tissues and cells that are related to a disrupted cGMP phosphodiesterase alpha subunit gene as claimed by the present invention. Thus, both Lem and Tanabe **fail to provide a suggestion or motivation to modify the references by generating a disrupted cGMP phosphodiesterase alpha subunit gene**. As such, both references are deficient in making a prima facie case of obviousness.

Baehr et al. has been cited for its description of the cDNA sequence of the cGMP phosphodiesterase alpha subunit gene. As acknowledged in the Office Action, the reference is not concerned with knockout or transgenic mice (nor is it concerned with targeting constructs, tissues, cells, and methods as recited in the pending claims). In other words, Baehr et al. does not disclose knockout mice, much less a knockout mouse with a disruption in a cGMP phosphodiesterase alpha subunit gene. As such, Baehr et al. does not contain any teaching or suggestion to make a transgenic mouse having a disruption in a cGMP phosphodiesterase alpha

subunit gene. Thus, Baehr et al. fails to make up the fundamental deficiencies of the Lem and Tanabe references. Because the basic criteria, cited in MPEP § 2142, has not been met, the Applicants respectfully submit that a proper showing of a prima facie case of obviousness has not been established. Therefore, the Applicants respectfully submit that the present invention is not obvious.

Conclusion

In view of the above amendments and remarks, the application is in good and proper form for allowance and the Examiner is respectfully requested to withdraw the rejections and pass this application to issue. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 569-5100.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1271, order number R-849.

Respectfully submitted,
DELTAGEN, INC.

Date: Sept. 13, 2002

By: Nicole A. Verona
Nicole A. Verona
Registration No. 47,153

DELTAGEN, INC.
740 Bay Road
Redwood City, CA 94063
Telephone: (650) 569-5100

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10)

I hereby certify that this correspondence and its listed enclosures are being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: Assistant Commissioner for Patents, Box Amendment, Washington, D.C. 20231 on **September 13, 2002.**
Express Mail No.: **EV 007 606 832 US**

Signed: Deborah A. Mojarro Date: 9/13/02
Name: **Deborah A. Mojarro**

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please replace the paragraph at page 10, lines 29-32 with the following rewritten paragraph:

--Figure 3A is schematic depicting the pDG4 vector. The vector contains an ampicillin resistance gene, a neomycin (Neo^r) gene and a green fluorescent protein (GFP) gene. On each side of the Neo^r gene are two sites for ligation-independent cloning along with restriction enzyme recognition sites. The sequence of pDG4 is shown in Figure 3B-1 through 3B-2 and SEQ ID NO:2. --

In the Claims:

1. (Amended) A murine targeting construct comprising:
   a. a first polynucleotide sequence homologous to a target gene, wherein the target gene is a cGMP phosphodiesterase alpha subunit gene;
   [(c)] (b) a second polynucleotide sequence homologous to the target gene; and
   [(d)] (c) a selectable marker.

2. The targeting construct of claim 1, wherein the targeting construct further comprises a screening marker.

3. (Amended) A method of producing a murine targeting construct, the method comprising:
   (a) obtaining a first polynucleotide sequence homologous to a cGMP phosphodiesterase alpha subunit gene;
   (b) obtaining a second polynucleotide sequence homologous to a cGMP phosphodiesterase alpha subunit gene;
   (c) providing a vector comprising a selectable marker; and
   (d) inserting the first and second sequences into the vector, to produce the targeting construct.

4. (Amended) A method of producing a murine targeting construct, the method comprising:
   (a) providing a polynucleotide sequence homologous to a cGMP phosphodiesterase alpha subunit gene;
   (b) generating two different fragments of the polynucleotide sequence;
   (c) providing a vector having a gene encoding a selectable marker; and
   (d) inserting the two different fragments into the vector to form the targeting construct.

5. (Amended) A murine embryonic stem cell comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene.

6. (Canceled) The cell of claim 5, wherein the cell is a murine cell.

7. (Canceled) The cell of claim 5, wherein the cell is an embryonic stem cell.

8. (Amended) A [non-human] transgenic mouse [animal] comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene wherein said mouse exhibits a phenotype comprising an eye abnormality.

9. (Amended) A cell derived from the [non-human transgenic animal] mouse of claim 8.

10. (Amended) A method of producing a transgenic mouse comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene, the method comprising:
    (a) introducing the targeting construct of claim 1 into a cell;
    (b) introducing the cell into a blastocyst;
    (c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and
    (d) breeding the chimeric mouse to produce the transgenic mouse.

11. (Amended) A method of identifying an agent that modulates the expression of a cGMP phosphodiesterase gene, the method comprising:
    (a) providing a transgenic mouse [non-human transgenic animal] comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene, wherein the mouse exhibits a phenotype comprising an eye abnormality; and
    (b) administering an agent to the transgenic mouse [non-human transgenic animal]; and
    (c) determining whether the expression of cGMP phosphodiesterase in the transgenic mouse [non-human transgenic animal] is modulated.

12. (Amended) A method of identifying an agent that modulates the function of a cGMP phosphodiesterase gene, the method comprising:
    (a) providing a [non-human transgenic animal] transgenic mouse comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene;
    (b) administering an agent to the transgenic mouse [non-human transgenic animal]; and
    (c) determining whether the function of the disrupted cGMP phosphodiesterase gene in the transgenic mouse [non-human transgenic animal] is modulated.

13. (Amended) A method of identifying an agent that modulates the expression of cGMP phosphodiesterase, the method comprising:
    (a) providing a murine cell comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene;
    (b) contacting the cell with an agent; and
    (c) determining whether expression of the cGMP phosphodiesterase is modulated.

14. (Amended) A method of identifying an agent that modulates the function of [a] cGMP phosphodiesterase, the method comprising:
    (a) providing a murine cell comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene;
    (b) contacting the cell with an agent; and
    (c) determining whether function of the cGMP phosphodiesterase gene is modulated.

15. (Canceled) The method of claim 13 or claim 14, wherein the cell is derived form the non-human transgenic animal of claim 8.

16. (Canceled) An agent identified by the method of claim 11, claim 12, claim 13, or claim 14.

17. (Amended) [A] The transgenic mouse of claim 8, [comprising a disruption in an cGMP phosphodiesterase gene,] wherein the [transgenic mouse exhibits an] eye abnormality is a retinal abnormality.

18. (Amended) The transgenic mouse of claim 17, wherein the [eye] retinal abnormality is [a retinal abnormality] characterized by retinal degeneration or retinal dysplasia.

19. (Amended) The transgenic mouse of claim 18, wherein the [retinal abnormality is characterized by retinal degeneration or retinal dysplasia] transgenic mouse exhibits an absence of photoreceptor layers.

20. (Amended) The transgenic mouse of claim [19] 18, wherein the [transgenic mouse exhibits an absence of photoreceptor layers] eye abnormality is consistent with vision problems or blindness.

21. (Amended) The transgenic mouse of claim [17] 18, wherein the [eye abnormality is consistent with vision problems or blindness] retinal abnormality is consistent with retinitis pigmentosa.

22. (Amended) The transgenic mouse of claim [19] 17, wherein the eye [retinal] abnormality [is consistent with retinitis pigmentosa] comprises at least one of the following: thinning or vacuolation of the inner nuclear layer of the eye; thinning of the inner plexiform layer of the eye; loss of ganglion cell nuclei; gliosis of the nerve fiber layer; or attenuation of retinal vasculature.

23. (Amended) [The transgenic mouse of claim 17, wherein the eye abnormality comprises at least one of the following: thinning or vacuolation of the inner nuclear layer of the eye; thinning of the inner plexiform layer of the eye; loss of ganglion cell nuclei; gliosis of the nerve fiber layer; or attenuation of retinal vasculature.] A method of producing a transgenic mouse comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene, wherein the transgenic mouse comprises an eye abnormality phenotype, the method comprising:

(a) introducing a cGMP phosphodiesterase alpha subunit gene targeting construct into a cell;
(b) introducing the cell into a blastocyst;
(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and
(d) breeding the chimeric mouse to produce the transgenic mouse comprising a homozygous disruption in an cGMP phosphodiesterase gene.

24. (Canceled) The transgenic mouse of claim 17, wherein the transgenic mouse is heterozygous for a disruption in an cGMP phosphosdiesterase gene.

25. (Canceled) The transgenic mouse of claim 17, wherein the transgenic mouse is homozygous for a disruption in an cGMP phosphodiesterase gene.

26. (Amended) [A method of producing a transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene, wherein the transgenic mouse exhibits an eye abnormality, the method comprising:
(a) introducing an cGMP phosphodiesterase gene targeting construct into a cell;
(b) introducing the cell into a blastocyst;
(c) implanting the resulting blastocyst into a pseudopregnant mouse, wherein said pseudopregnant mouse gives birth to a chimeric mouse; and
(d) breeding the chimeric mouse to produce the transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene.]
A cell derived from the transgenic mouse of claim 8 or claim 23, wherein the cell comprises a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene.

27. (Amended) A method of identifying an agent that ameliorates an eye abnormality, the method comprising:
(a) administering an agent to a [A cell derived from the] transgenic mouse [of claim 17 or claim 26, wherein the cell] compris[es]ing a homozygous disruption in a[n] cGMP phosphodiesterase alpha subunit gene; [and wherein the transgenic mouse exhibits an eye abnormality]; and
(b) determining whether the agent ameliorates the eye abnormality of the transgenic mouse.

28. (Amended) [A method of identifying an agent that ameliorates an eye abnormality, the method comprising:
(a) administering an agent to a transgenic mouse comprising a disruption in an cGMP phosphodiesterase gene; and
(b) determining whether the agent ameliorates the eye abnormality of the transgenic mouse.] The method of claim 27, wherein the eye abnormality is a retinal abnormality.

29. (Amended) The method of claim 28, wherein the [eye] retinal abnormality is characterized by retinal degeneration or retinal dysplasia.

30. (Amended) The method of claim 29, wherein the [retinal abnormality is characterized by retinal degeneration or retinal dysplasia] transgenic mouse exhibits an absence of photoreceptor layers.

31. (Amended) The method of claim [28] 27, wherein the [transgenic mouse exhibits an absence of photoreceptor layers] eye abnormality comprises at least one of the following: thinning or vacuolation of the inner nuclear layer of the eye; thinning of the inner plexiform layer of the eye; loss of ganglion cell nuclei in the eye; gliosis of the nerve fiber layer of the eye; or attenuation of retinal vasculature in the eye.

32. (Amended) [The method of claim 28, wherein the eye abnormality comprises at least one of the following: thinning or vacuolation of the inner nuclear layer of the eye; thinning of the inner plexiform layer of the eye; loss of ganglion cell nuclei in the eye; gliosis of the nerve fiber layer of the eye; or attenuation of retinal vasculature in the eye.] A method of identifying an agent which modulates cGMP phosphodiesterase expression, the method comprising:
    (a) administering an agent to a transgenic mouse comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene, wherein the transgenic mouse comprises a phenotype comprising an eye abnormality; and
    (b) determining whether the agent modulates cGMP phosphodiesterase expression in the transgenic mouse, wherein a modulation of the phenotype is indicative of a modulation of cGMP phosphodiesterase expression.

33. (Amended) A method of identifying an agent which modulates a phenotype comprising an eye abnormality, wherein the phenotype is associated with a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene [expression], the method comprising:
    (a) administering an agent to a transgenic mouse comprising a homozygous disruption in a[n] cGMP phosphodiesterase alpha subunit gene; and
    (b) determining whether the agent modulates [cGMP phosphodiesterase expression in the transgenic mouse, wherein the agent modulates a phenotype associated with a disruption in an cGMP phosphodiesterase gene] the phenotype.

34. (Canceled) The method of claim 33, wherein the phenotype comprises an eye abnormality.

35. (Amended) A method of identifying an agent which modulates a phenotype associated with a disruption in an cGMP phosphodiesterase gene, the method comprising:
    (a) administering an agent to a transgenic mouse comprising a homozygous disruption in an cGMP phosphodiesterase gene, wherein said mouse exhibits an eye abnormality or hyperactivity; and
    (b) determining whether the agent modulates the phenotype.

36. (Canceled) The method of claim 35, wherein the phenotype comprises an eye abnormality.

37. (Amended) A method of identifying an agent which modulates cGMP phosphodiesterase expression, the method comprising:
    (a) providing a murine cell comprising a homozygous disruption in cGMP phosphodiesterase alpha subunit gene;
    (b) contacting the cell with an agent; and
    (c) determining whether the agent modulates cGMP phosphodiesterase expression, wherein [the agent] modulat[es]ion of a phenotyp[e]ic abnormality comprising an eye abnormality is indicative of an agent that modulates the expression of a [associated with a disruption in an] cGMP phosphodiesterase gene.

38. (Canceled) The method of claim 37, wherein the phenotype comprises an eye abnormality.

39. (Amended) A method of identifying an agent which modulates cGMP phosphodiesterase gene function, the method comprising:
    (a) providing a murine cell comprising a homozygous disruption in an cGMP phosphodiesterase alpha subunit gene;
    (b) contacting the cell with an agent; and
    (c) determining whether the agent modulates cGMP phosphodiesterase gene function, wherein [the agent] modulat[es]ion of a phenotyp[e]ic abnormality comprising an eye abnormality is indicative of an agent that modulates the function of a [associated with a disruption in an] cGMP phosphodiesterase gene.

40. (Canceled) The method of claim 39, wherein the phenotype comprises an eye abnormality.

41. (Canceled) An agent identified by the method of claim 28, claim 33, claim 35, claim 37 or claim 39.

42. (Amended) A transgenic mouse comprising a homozygous disruption in an cGMP phosphodiesterase alpha subunit gene, wherein the transgenic mouse exhibits a phenotype comprising hyperactive behavior.

43. (Canceled) The transgenic mouse of claim 42, wherein the transgenic mouse is heterozygous for a disruption in an cGMP phosphodiesterase gene.

44. (Canceled) The transgenic mouse of claim 43, wherein the transgenic mouse is homozygous for a disruption in an cGMP phosphodiesterase gene.

45. (Amended) A method of identifying an agent that ameliorates hyperactive behavior, the method comprising:
    (a) administering an agent to a transgenic mouse comprising a homozygous disruption in an cGMP phosphodiesterase alpha subunit gene; and
    (b) determining whether the agent ameliorates hyperactive behavior of the transgenic mouse.

46. (Amended) A method of identifying an agent which modulates [an] cGMP phosphodiesterase expression, the method comprising:
    (a) administering an agent to the transgenic mouse comprising a homozygous disruption in a[n] cGMP phosphodiesterase alpha subunit gene; and
    (b) determining whether the agent modulates cGMP phosphodiesterase expression in the transgenic mouse, wherein the agent has an effect on hyperactive behavior of the transgenic mouse.

47. (Amended) A method of identifying an agent which modulates a phenotype associated with a disruption in a cGMP phosphodiesterase gene, the method comprising:
    (a) administering an agent to a transgenic mouse comprising a homozygous disruption in a cGMP phosphodiesterase alpha subunit gene; and
    (b) determining whether the agent modulates hyperactive behavior of the transgenic mouse.

48. (Canceled) An agent identified by the method of claim 45, claim 46 or claim 47.